Remarks

Status of the specification and claims

Claims 36-75 are currently pending. The specification and claims 36-54 and 58-66 stand rejected under §112, first paragraph as failing to provide an enabling disclosure. Claims 36-54 and 58-66 stand rejected under §112, second paragraph, as being indefinite. Claims 36-73 stand rejected under §103 as unpatentable over Partis,[1] Chang,[2] Applicants' admissions on the record, and Gish.[3]

Claim 36 has been cancelled. Claims 37, 38, 43, 53-56, 58, 61, and 65 have been amended to depend from claim 70. The definition of R has been amended in claims 38-41, 43-46, 53, 54, 66, 70, and 71. Claim 55 has been amended to depend from claim 73, to delete an N-substituted DNJ compound outside the scope of claim 73, and to correct an obvious typographical error. Claims 73 and 75 have also been amended to correct typographical errors. Support for the amendments to the claims may be found, for example, at pages 12-14 of the specification.

Clarification of the status of claims 74 and 75 is respectfully requested. Claims 74 and 75 were added by the amendment filed on December 16, 2002. The Office noted that this amendment has been received and entered into the file; however, the Office has not indicated whether claims 74 and 75 are allowable.

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[1] Partis et al., U.S. Patent No. 5,221,746.

[2] Chang et al., U.S. Patent No. 5,750,648.

[3] Gish et al., Exp. Opin. Invest. Drugs (1995) 4:95-115.

Objection to the specification and claims 36-54 and 58-66 under §112, first paragraph

Reconsideration is requested of the objection to the specification, and the rejection of claims 36-54 and 58-66, under §112, first paragraph, as failing to provide an enabling disclosure.

The Office asserts that the specification is not enabling because it does not "set forth the criteria that defines an 'antiviral compound'" and that the specification does not "provide information allowing the skilled artisan to ascertain these compounds without undue experimentation."

Applicants respectfully disagree with the Office's assertion that the specification does not satisfy the requirements of §112, first paragraph. The definition of the phrase "antiviral compound" is well-recognized in the art, and the phrase does not require further definition or criteria. For example, attached as **Appendix A** is an excerpt from *Dorland's Medical Dictionary*, which defines "antiviral" as:

> 1. destroying viruses or suppressing their replication.
> 2. an agent that destroys viruses or suppresses their replication.

As those skilled in the art understand, antiviral nucleosides and nucleotides function at least to suppress replication of viruses, if not to destroy them. The exact mechanism by which the suppression occurs may vary depending on the identity of the nucleoside or nucleotide and the virus against which it is administered, but generally these compounds are known to be effective in suppressing replication at one or more stages in the attack of a virus upon a host cell or use by the virus of cell biochemistry for its reproduction.

Whether a particular compound has activity against a particular virus, in this case hepatitis virus, is readily

determined by one skilled in the art. Numerous *in vitro* antiviral assays wherein the efficacy of a particular compound in inhibiting one or more hepatitis viruses or virus strains are available. The specification provides an example of such an assay, see Example 3, and others are known in the art as of the filing date of the instant application. These assays are readily available and routinely used. Similarly, *in vivo* antiviral assays such as the woodchuck animal model known in the art and described in Examples 4 and 5, and other animal models known to those skilled in the art (e.g., Peking duck and California ground squirrel models) are available.[4] By using of one or more of these assays, a skilled artisan can readily determine whether particular nucleosides, nucleotides, or mixtures thereof described in the specification, are antiviral compounds.

Moreover, the specification describes in detail the class of nucleosides and nucleotides. Indeed, the Office has acknowledged that "[b]ased on the instant disclosure, the skilled artisan would have no problem identifying those compounds falling into the classes of nucleotide[s], or nucleosides envisioned by Applicants."[5]

While the pharmaceutical art may be somewhat unpredictable, assays available to determine whether a particular compound is an antiviral compound are routinely performed by skilled artisans. The mere fact that some experimentation may be necessary to select antiviral compounds not named in the specification does not render the specification non-enabling:

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[4] See, e.g., Tennant et al., "Animal Models in the Preclinical Assessment of Therapy for Viral Hepatitis," *Antiviral Therapy* (1996), 1 (Suppl. 4, Therapies for Viral Hepatitis), 47-52, an abstract of which is attached hereto as **Appendix B**.

[5] See Paper no. 10, page 7.

> 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'[6]

The *in vitro* assays described in the specification and known to those skilled in the art are routine assays. The specification does describe antiviral nucleoside and nucleotide compounds that are useful in the invention, as the Office has acknowledged. One skilled in the art could perform the routine assays described in the specification to determine other antiviral nucleosides and nucleotides useful in the invention without undue experimentation.

For the foregoing reasons, Applicants assert that the specification satisfies the requirements of §112, first paragraph. Claim 36 has been cancelled, rendering moot its rejection under §112, first paragraph. For the same reasons given above with respect to the specification, claims 37-54 and 58-66 also satisfy the requirements of §112, first paragraph.

Rejection of claims 36-54 and 58-66 under §112, second paragraph

Reconsideration is requested of the rejection of claims 36-54 and 58-66 under §112, second paragraph, as being indefinite.

Claim 36 has been cancelled, rendering moot its rejection under §112, second paragraph.

The Office asserts that claims 37-54 and 58-66 fail to clearly set forth the metes and bounds of the patent protection desired due to reference to "antiviral compounds," and that the specification does not provide criteria that define medicaments that "fall under the 'antiviral compound' penumbra." As discussed above, however, the definition of the phrase "antiviral compound"

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[6] MPEP 2164.06, citing In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

is well-recognized in the art, and the phrase does not require further definition or criteria. Whether a particular compound has activity against a particular virus, in this case hepatitis virus, is readily determined by one skilled in the art, who can make use of any number of *in vitro* or *in vivo* assays available in the art, and known to skilled artisans, at the time the instant application was filed. Moreover, the claims do not recite antiviral compounds generically, but is limited to antiviral compounds that are nucleosides, nucleotides, or mixtures thereof.

MPEP 2173.02 requires that definiteness of a claim be analyzed in light of the disclosure of the instant application, the teachings of the prior art and the claim interpretation that would be given by one of ordinary skill in the art at the time the invention was made. Analyzed in this light, the phrase "antiviral compound" does not render claims 37-54 and 58-66 indefinite, and these claims satisfy the requirements of §112, second paragraph.

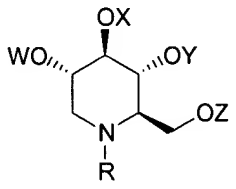
Rejection of claims 36-73 under §103

Reconsideration is requested of the rejection of claims 36-73 under §103 as unpatentable over Partis, Chang, Applicants' admissions on the record, and Gish.

Claim 36 has been cancelled, rendering moot its rejection under §103.

Seven independent claims (claims 66 and 69-74) are pending; claim 70 is representative of these independent claims. As amended, claim 70 is directed to a pharmaceutical composition comprising a first amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, and a pharmaceutically acceptable carrier,

diluent, or excipient. N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compounds are also known as N-substituted DNJ compounds. The compound of Formula I has the following structure:



I

Claim 70 defines R as selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having seven or more carbon atoms; W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl.

Partis discloses O-acylated DNJ derivatives, and their N-alkyl, N-acyl and N-aroyl derivatives. These compounds are described as inhibitors of visna virus (and potentially HIV), cytomegalovirus, and/or the α- and β-glucosidases.[7] Nowhere does Partis disclose or suggest that the DNJ derivatives described inhibit hepatitis virus. Furthermore, nowhere does Partis describe or suggest the combination of any of the N-substituted DNJ compounds described with a nucleoside or a nucleotide antiviral compound, as required in claim 70.

Gish discloses a long list of agents for the treatment of chronic HBV infection, including immune modulating agents, vaccines, herbal therapy, nucleoside analogues, synthetic oligodeoxyribonucleotides, antisense molecules and decoys. Gish presents a general discussion of the potential benefits of combination therapies, and remarks that "the future use of immunomodulating agents such as interferon or interleukin with a nucleoside analogue appears promising."[8] Nowhere does Gish so

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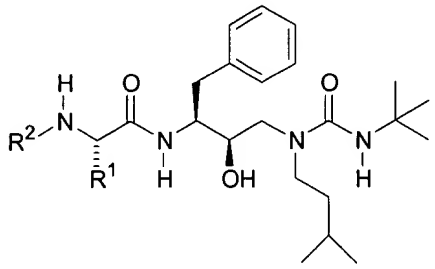
[7] See col. 6, lines 1-29.

[8] See page 107.

much as mention DNJ or any N-substituted derivative, either alone or in combination with any anti-hepatitis agent. He utterly fails to suggest the combination of a DNJ derivative with any other agent for the treatment of hepatitis.

Chang fails to supply what is missing in Partis' and Gish's disclosure. Chang discloses novel HIV-protease inhibitors and their use in the treatment of HIV infection. The protease inhibitors have the following structure:



wherein R^1 and R^2 are as defined in the reference.

The Office apparently relies on Chang not for his primary teaching, but for further disclosure of the administration of combinations of the protease inhibitors he describes "with two or three other antiviral agents which are effective against HIV-1,"[9] including other HIV-1 protease inhibitors, various nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, tat antagonists, and glycosidase inhibitors.[10] Among the nucleoside analogs that can be used in combination with a protease inhibitor for treatment of HIV are AZT, DDI, DDC, 3TC, D4T, and PMEA.[11] N-butyl DNJ and its per-butyl ester are named as examples of glycosidase inhibitors.[12]

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[9] See col. 33, lines 24-26.

[10] Id. at col. 33, lines 23-26.

[11] Id. at col. 33, lines 57-58.

[12] Id. at col. 34, lines 14-19.

Whatever Chang may teach about combining a protease inhibitor having the formula shown above with two or three other antiviral agents that are effective against HIV-1, Chang does not teach or even suggest the particular combination of an N-substituted DNJ compound as defined in claim 70 and an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, for any purpose whatsoever. That is, Chang may separately suggest the combination of the protease inhibitor with a nucleoside or nucleotide, or the combination of a protease inhibitor with N-butyl DNJ, but nowhere does Chang suggest the particular combination of N-butyl DNJ with either a nucleoside or a nucleotide. Only by gross exercise of hindsight would one skilled in the art select the combination of a nucleoside antiviral compound, a nucleotide antiviral compound, or mixtures thereof, and an N-substituted DNJ derivative for combination according to the claimed compositions.

As acknowledged by Applicants and as stated in the specification, DNJ and its N-alkyl derivatives are known inhibitors of the N-linked oligosaccharide processing enzymes alpha glucosidase I and II,[13] and have potential to inhibit glucose transport, glucosyl-transferases, and/or glycolipid synthesis.[14] Applicants have further acknowledged that N-alkyl-DNJ compounds wherein the alkyl group has from three to six carbons have been shown to be effective in the treatment of hepatitis B infection.[15]

The Office has failed to establish that claims 37-73 are *prima facie* obvious over the prior art. The Office asserts that

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[13] See Specification, page 2, lines 30-35.

[14] Id. at page 2, line 35 through page 3, line 5.

[15] Id. at page 3, lines 11-20.

it is "*prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose." However, none of Gish, Chang, and Partis disclose or suggest that the N-substituted DNJ compounds within the scope of amended claim 70 are active against hepatitis virus. Nor have Applicants admitted that these N-substituted DNJ compounds were known in the art as hepatitis inhibitors. Applicants have acknowledged that N-alkyl DNJ derivatives are known inhibitors of the N-linked oligosaccharide processing enzymes alpha glucosidase I and II, and that as glucose analogs, they have potential to inhibit glucose transport, glucosyl-transferases, and/or glycolipid synthesis. Applicants have not, however, acknowledged that the N-substituted DNJ compounds described in claims 37-73 were known in the art as anti-hepatitis compounds.

In fact, none of the cited references disclose any N-substituted-DNJ compounds as active against hepatitis virus. As noted above, Gish does not disclose any N-substituted-DNJ compounds. The primary thrust of the Chang patent is the provision of urea-containing hydroxyethylamine protease inhibitors for the treatment of HIV. While Chang does mention N-butyl DNJ and its per-butyl ester, it is in the context of antiviral agents effective against HIV-1. Furthermore, N-butyl DNJ and its per-butyl ester is outside the scope of claim 70 as amended. The O-acylated DNJ derivatives described by Partis are described as having inhibitory activity against visna virus, a model of HIV inhibitory activity.[16] Applicants have selected N-substituted DNJ compounds not previously disclosed as having anti-hepatitis virus activity and have combined them with

[16] See col. 6, lines 1-15.

nucleoside and/or nucleotide antiviral compounds to prepare the compositions of the instant claims.

To establish that a claim is *prima facie* obvious in view of the prior art, the Office must show that the prior art reference(s) teach or suggest all the claim limitations, and that there is a motivation in the art to combine the references with a reasonable expectation of success. With regard to amended claim 70, the Office has not met even the first hurdle, i.e., the PTO has not shown that the compositions of claim 70 are taught or suggested by any of Gish, Partis, Chang, or Applicants' admissions on the record, taken alone or together. The Office has not because it cannot.

Furthermore, the actual teachings of Gish, Partis, and Chang particularly fail to make it obvious to select the N-substituted-DNJ compounds and the nucleoside or nucleotide antiviral compounds of claim 70, out of the many agents that individually show activity against hepatitis virus (see, e.g., Gish) and to combine these compounds in compositions. Among the many compositions proposed in the art for treatment of hepatitis infections, the cited references offer no guidance that would have enabled one skilled in the art to select the N-substituted-DNJ compounds described in claim 70 for combination with nucleoside or nucleotide antiviral compounds in general, as in claims 37-54, 58-66, 70 and 71, or with the particular antiviral compounds of, for example, claims 55-57, 67-69, 72 and 73. Applicants, on the other hand, selected N-substituted-DNJ compounds not disclosed in the cited art for treatment of hepatitis infections; selected nucleoside or nucleotide antiviral compounds from the many antiviral compounds known in the art; chose further to administer the N-substituted DNJ compounds in combination with nucleosides, nucleotides, or mixtures thereof;

formulated a composition comprising the same; and have demonstrated the efficacy of the combination therapy for inhibiting hepatitis virus.[17]

Lastly, the Office maintains that "[t]o employ an analog, homolog, isomer, bioisostere, salts acid and ester for the same use therapeutic use [sic] would have been obvious to the skilled artisan."[18] The Office further maintains that the "[p]rior art use for the same therapeutic purpose would have motivated the skilled artisan to employ N-alkyl derivatives of deoxynojirmycin(as specifically taught by Partis et al (see examples 13 and 16) for treating viral diseases and enjoy a reasonable expectation of therapeutic success."[19] Applicants respectfully disagree. While it is true that Partis disclose N-substituted DNJ compounds within the scope of claim 70, as amended, these compounds (namely, N-nonyl-DNJ and its tetraacetate ester)[20] are not disclosed as inhibitors of hepatitis virus, but of HIV. One skilled in the art would not expect that a particular compound that is active against HIV would also be active against hepatitis virus. HIV and hepatitis virus are members of different viral families (*Retroviridae* and *Hepadnaviridae*, respectively), and the skilled artisan would not expect the same compound to inhibit viruses from different viral families. The art neither suggests the use of N-substituted-DNJ compounds in combination with nucleosides or nucleotides to treat hepatitis infection, otherwise provides any motivation to make such combination, nor provides any reasonable basis for expecting that the combination would offer any benefit or advantage.

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[17] See Specification, Example 3.

[18] See Paper no. 15, page 6.

[19] Id.

[20] See col. 11, Examples 13 and 14.

For the foregoing reasons, it is respectfully submitted that the Office has not established that claim 70, or claims 37-65, which depend from claim 70, are *prima facie* obvious in view of Gish, Partis, Chang, or Applicants' admissions on the record, taken alone or together.

Claim 66, as amended, is directed to a pharmaceutical composition for treating a hepatitis B virus infection in a mammal, comprising from about 0.1 mg to about 100 mg of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I as shown above and from about 0.1 mg to about 500 mg of a compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral, and mixtures thereof. Claim 66 defines R as selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having a chain length of C_7 to C_{20}. W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl.

Claim 69 is directed to a pharmaceutical composition for treating a hepatitis B virus infection in a human patient, comprising from about 0.1 mg to about 100 mg of N-(n-nonyl-)-1,5-dideoxy-1,5-imino-D-glucitol and from about 0.1 mg to about 500 mg of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate.

Claim 71, as amended, is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I, a second amount of an antiviral compound, and a pharmaceutically acceptable carrier, diluent, or excipient. Claim 71 defines R as selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having a chain length of between C_7 and C_{20}, and W, X, Y, and Z are as defined in the claim. The antiviral compound is selected

from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof.

Claim 72 is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I (having the structure shown above), a second amount of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC), and a pharmaceutically acceptable carrier, diluent, or excipient. Claim 72 defines R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having seven or more carbon atoms, and W, X, Y, and Z are as defined in the claim.

Claim 73 is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I (having the structure shown above), a second amount of an antiviral compound selected from a group consisting of thirty-five specific compounds, and a pharmaceutically acceptable carrier, diluent, or excipient. Claim 73 defines R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having seven or more carbon atoms, and W, X, Y, and Z are as defined in the claim.

For the same reasons given above with respect to claim 70, the Office has not established that any of claims 66, 69, or 71-73 are *prima facie* obvious in view of Gish, Partis, Chang, or Applicants' admissions on the record, taken alone or together.

Conclusion

In light of the foregoing remarks, it is respectfully submitted that the specification and claims 37-54 and 58-66 satisfy the requirements of §112, and that claims 37-73 satisfy the requirements of §103. Favorable reconsideration and early allowance of all claims are respectfully requested.

If there are any additional charges in this matter, please charge Deposit Account No. 19-1345.

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Twenty-sixth Edition

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antithyrotoxic (an"ti-thi"ro-tok'sik) counteracting the toxic effect of thyroid and thyroid products.

antithyrotropic (an"ti-thi"ro-trop'ik) inhibiting the action of the thyrotropic hormone.

antitonic (an"ti-ton'ik) reducing tone or tonicity.

antitoxic (an"ti-tok'sik) effective against a poison; pertaining to antitoxin.

antitoxigen (an"ti-tok'si-jen) [*antitoxin* + Gr. *gennan* to produce] any substance that induces the formation of antitoxin in the animal body; antitoxinogen.

antitoxin (an"ti-tok'sin) [*anti-* + Gr. *toxicon* poison] antibody to the toxin of a microorganism (usually the bacterial exotoxins), to a zootoxin (e.g., spider or bee venom), or to a phytotoxin (e.g., ricin of the castor bean), which combines specifically with the toxin, in vivo and in vitro, with neutralization of toxicity. **botulinal a., botulinum a., botulinus a.,** botulism a. [USP], a sterile solution of antitoxic substances (antibodies) from the blood serum or plasma of healthy horses immunized against the toxins of *Clostridium botulinum*, used as a passive immunizing agent. It is available in bivalent (types A and B), trivalent (types A, B, and E), and monovalent (type E) forms. Called also *botulinum* a. and *botulinus* a. **bovine a.,** antitoxin containing antibodies derived from the cow instead of from the horse, for use on persons who are hypersensitive to horse serum. **diphtheria a.** [USP], a sterile solution of refined and concentrated antibody globulins derived from the blood serum or plasma of a healthy animal, usually the horse, immunized against diphtheria toxins; used as a passive immunizing agent, administered intramuscularly or intravenously. **gas gangrene a.,** a sterile solution of antibody globulins from the blood of horses immunized against the toxins of certain species of pathogenic clostridia. Bivalent antitoxin contains antibodies against *Clostridium perfringens* and *Cl. septicum*; trivalent contains these plus antibodies against *Cl. novyi*. Antibodies against *Cl. histolyticum* and *Cl. bifermentans* are added to these in polyvalent antitoxins. **normal a.,** antitoxin capable of neutralizing an equal quantity of normal toxin solution. **scarlet fever streptococcus a.,** a sterile solution of antitoxic substances (i.e., immunoglobulins) from blood serum of healthy animals immunized against toxin from the streptococci causing scarlet fever. **tetanus a.** [USP], a sterile solution of refined and concentrated antibody globulins obtained from the blood serum or plasma of a healthy animal, usually the horse, immunized against tetanus toxin or toxoid; used as a passive immunizing agent, administered intramuscularly, subcutaneously, or intravenously. **tetanus and gas gangrene a's,** a sterile solution of antitoxic substances (immunoglobulins) obtained from the blood of healthy animals immunized against the toxins of *Clostridium tetani*, *C. perfringens*, and *C. septicum*, used for prophylactic immunization against tetanus.

antitoxinogen (an"ti-tok-sin'o-jen) [*antitoxin* + Gr. *gennan* to produce] an antigen that stimulates the production of antitoxin.

antitoxinum (an"ti-tok-si'num) [L.] antitoxin.

antitragicus (an"ti-traj'o-kus) see *Table of Musculi*.

antitragus (an"ti-tra'gus) [*anti-* + *tragus*] [NA] a projection opposite the tragus, bounding the cavum concheae posteroinferiorly and continuous above with the anthelix.

antitreponemal (an"ti-trep"o-ne'mal) 1. effective against *Treponema*. 2. an agent that is effective against *Treponema*.

antitrichomonal (an"ti-trich"o-mo'nal) 1. effective against *Trichomonas*. 2. an agent that is destructive to *Trichomonas*.

antitrismus (an"ti-tris'mus) a spasm that prevents the closure of the mouth.

antitrope (an'ti-trop) [*anti-* + Gr. *trepein* to turn] 1. any organ that forms a symmetrical pair with another. 2. antibody.

antitropic (an"ti-tro'pic) corresponding, but oppositely oriented, as a right and a left glove.

antitropin (an"ti-tro'pin) any substance that opposes the action of tropin; antiopsonin.

antitrypanosomal (an"ti-tri-pan"o-so'mal) 1. effective against trypanosomes. 2. a drug for combating trypanosomiasis.

antitrypsic (an"ti-trip'sik) antitryptic.

α_1-antitrypsin (an"ti-trip'sin) alpha$_1$-antitrypsin.

antitryptase (an"ti-trip'tās) a substance that inhibits or counteracts the action of tryptase.

antitryptic (an"ti-trip'tik) [*anti-* + *tryptic*] counteracting the activity of trypsin.

antituberculin (an"ti-tu-ber'ku-lin) an antibody developed following the injection of tuberculin into the animal body.

antituberculotic (an"ti-tu-ber"ku-lot'ik) 1. therapeutically effective against tuberculosis. 2. an agent that is therapeutically effective against tuberculosis.

antituberculous (an"ti-tu-ber'ku-lus) therapeutically effective against tuberculosis.

antitubulin (an"ti-too'bu-lin) an agent that prevents the polymerization of tubulin, and thus the formation of microtubules in a cell.

antitumorigenic (an"ti-tu"mor-i-jen'ik) counteracting tumor formation.

antitussive (an"ti-tus'iv) 1. relieving or preventing cough. 2. an agent that relieves or prevents cough.

antityphoid (an"ti-ti'foid) counteracting or preventing typhoid.

antityrosinase (an"ti-ti-ro'si-nās) an antienzyme that counteracts tyrosinase.

antiulcerative (an"ti-ul'ser-a"tiv) 1. preventing or promoting the healing of ulcers. 2. an agent that so acts.

antiuratic (an"ti-u-rat'ik) preventing the deposit of urates.

antiurease (an"ti-u're-ās) an antibody that inhibits the activity of urease.

antiurokinase (an"ti-u"ro-ki"nās) a naturally occurring substance that inhibits clot dissolution by inhibiting the action of urokinase.

antivaccinationist (an"ti-vak"si-na'shun-ist) a person who is opposed to vaccination.

antivenene (an"ti-vē-nēn') [*anti-* + L. *venenum* poison] antivenin.

antivenereal (an"ti-vē-ne're-al) effective against venereal disease.

antivenin (an"ti-ven'in) [*anti-* + L. *venenum* poison] a proteinaceous material used in the treatment of poisoning by animal venom. See also *antivenomous serum*, under *serum*. **black widow spider a.,** *Latrodectus mactans* a. **Latrodectus mactans a.,** an antitoxic serum specific in the treatment of black widow spider (*L. mactans*) bites, prepared by immunizing horses against venom of the black widow spider; called also *black widow spider a.* **a. (*Micrurus fulvius*)** [USP], a sterile, nonpyrogenic preparation derived by drying a frozen solution of specific venom-neutralizing globulins obtained from serum of horses immunized against the venom of Eastern coral snakes (*Micrurus fulvius*). **a. (Crotalidae) polyvalent** [USP], **polyvalent crotaline a.,** a sterile serum containing specific venom-neutralizing globulins, produced by hyperimmunization of horses with the venoms of the fer-de-lance and the Florida, Texas, and tropical rattlesnake; used as a passive immunizing agent for the treatment of envenomation by most pit vipers throughout the world.

antivenom (an"ti-ven'om) antivenin.

antivenomous (an"ti-ven'o-mus) counteracting venom.

antiviral (an"ti-vi'ral) 1. destroying viruses or suppressing their replication. 2. an agent that destroys viruses or suppresses their replication.

antivirotic (an"ti-vi-rot'ik) 1. antiviral. 2. an agent that destroys viruses or checks their growth or multiplication.

antivirulin (an"ti-vir'u-lin) any substance that opposes the action of virulin; the substance in animals immunized against rabies, which neutralizes or inactivates the virus of rabies.

antivirus (an"ti-vi'rus) Besredka's name for the filtered and heated broth cultures of bacteria used by him to produce local immunity.

antivitamer (an"ti-vi'tah-mer) a substance that inactivates a vitamer.

antivitamin (an"ti-vi'tah-min) a substance that inactivates a vitamin.

antivivisection (an"ti-viv"i-sek'shun) opposition to vivisection.

antivivisectionist (an"ti-viv"i-sek'shun-ist) an individual opposed to vivisection.

antixenic (an"ti-ze'nik) [*anti-* + Gr. *xenos* strange or foreign] pertaining to the reaction of living tissue to any foreign substance.

antixerophthalmic (an"ti-ze"rof-thal'mik) counteracting xerophthalmia.

antixerotic (an"ti-ze-rot'ik) counteracting or preventing xerosis.

antizyme (an'ti-zim) a protein whose synthesis is induced by a product of an enzyme reaction and which combines with and inhibits the action of that enzyme.

antizymohexase (an"ti-zi"mo-hek'sās) an antienzyme that counteracts zymohexase.

antizymotic (an"ti-zi-mot'ik) inhibiting or suppressing the action of enzymes.

antodontalgic (an"to-don-tal'jik) antiodontalgic.

Anton's symptom (syndrome) (an'tons) [Gabriel *Anton*, German neuropsychiatrist, 1858–1933] see under *symptom*.

antophthalmic (ant"of-thal'mik) relieving ophthalmia.

antorphine (an-tor'fēn) nalorphine.

antra (an'trah) [L.] plural of *antrum*.

antracele (an'trah-sēl) antrocele.

antral (an'tral) of or pertaining to an antrum.

antrectomy (an-trek'to-me) [*antrum* + Gr. *ektomē* excision] surgical excision of an antrum, as resection of the pyloric antrum of the stomach.

Antrenyl (an'trē-nil) trademark for a preparation of oxyphenonium.